## REMARKS

As a result of the above amendments, claims 51-81 are currently pending. Claims 1, 3, 4, 6-11, 13, 14, 16-21, 23, 24, 26-31, 33, 34, and 36-42 are cancelled without prejudice to the prosecution of cancelled subject matter in other patent applications. None of the amendments constitute new matter.

Claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41, and 42 are rejected under the first paragraph of 35 U.S.C. §112 for allegedly failing to comply with the written description requirement.

Claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41, and 42 are rejected under the first paragraph of 35 U.S.C. §112 for allegedly lacking enablement for the full scope of the claims.

Claims 1, 3, 4, 6, 7, 8, 9, 10, 11, 13, 14, 16, 17, 18 and 19 are rejected under the doctrine of obviousness-type double patenting.

Claims 1, 3, 4, 6, 7, 8, 9, 10, 11, 13, 14, 16, 17, 18 and 19 are rejected under 35 U.S.C. §103 as allegedly being obvious.

For reasons set forth herein, the rejections should be removed and the claims should be deemed allowable.

### 1. The Claims Comply With The Written Description Requirement

Claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41, and 42 are rejected under 35 U.S.C. §112 for failing to comply with the written description requirement. In particular, the Examiner notes that the specification encompasses functional equivalents of the nucleic acid encoding MDA-7 protein. The

Examiner suggests that in order to provide adequate written description of a claimed genus, the specification must provide distinguishing identifying characteristics of the genus, including, among other characteristics, "physical and/or chemical properties" or "functional characteristics."

The replacement claims remedy the Examiner's objection by providing adequate identifying characteristics of the present invention. More particularly, the replacement claims provide a detailed description of the function and properties of the hybridizing nucleic acid. The known nucleic acid sequence encoding *MDA-7*, residues 275 to 895 of SEQ ID NO: 1, is claimed, as are other nucleic acids that either encode a protein having SEQ ID NO: 2 or that hybridize to SEQ ID NO: 1 under stringent conditions and encode a protein known to function as *MDA-7*. "Stringent hybridization conditions" are defined as hybridization in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM ethylenediamine tetraacetic acid (EDTA) at 65°C, and washing in 0.1x standard saline citrate (SSC)/0.1% SDS at 68°C. Further, the functional property, the ability to inhibit proliferation of melanoma cells, is now recited in the replacement claims. Therefore, it is requested that the rejection not be maintained or applied to the newly-added replacement claims. The inclusion of precise hybridization conditions and functional properties in the novel claims is sufficient to satisfy the written description requirement of 35 U.S.C. §112.

2. **The Claims Are Enabled**

Claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41, and 42 are further objected to under 35 U.S.C. §112 as failing to comply with the

enablement requirement. The Examiner states that the specification, while being enabling for:

> A method for inhibiting proliferation of cancer cells wherein said cancer cells comprise a mutated *ras* gene that increases *RAS* activity in the cancer cell, wherein said method comprises directly administering to said cancer cells a composition comprising:
> (i) a nucleic acid that encode and expresses the polypeptide of SEQ ID NO: 2 (MDA-7), and
> (ii) a nucleic acid molecule that specifically hybridizes under stringent conditions to a *RAS* nucleic acid molecule and that inhibits translation of *ras*-specific mRNA;
>
> does not provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In particular, the Examiner states that the claims are not enabled because (i) they are not limited as to route of administration; (ii) they cover a wide range of variants of SEQ ID NO: 1; (iii) the treated cells are not required to exhibit increased *RAS* activity; and (iv) as regards claims 41 and 42, the treated cells are not required to contain a mutated *ras* gene.

The newly-added claims are fully enabled by the specification. The newly-added replacement claims address bases (ii)-(iv) of the enablement rejection, thereby rendering these bases moot. Therefore, the only remaining issue is the route of administration of the therapeutic agent of the present invention.

In the previous response, Applicant submitted three published articles as evidence of enablement, namely (1) Ramesh *et al.*, 2004, "Local and systemic inhibition of lung tumor growth after nanoparticle-mediated mda-7/IL-24 gene delivery," DNA Cell Biol. 23(12):850-857, (2) Tong *et al.*, 2005, "Intratumoral injection of INGN 241, a nonreplicating adenovector expressing the melanoma-differentiation associated gene-7

(mda-7/IL24): biologic outcome in advanced cancer patients," Mol. Ther. 11(1):160-172, and (3) Cunningham *et al.*, 2005, "Clinical and local biological effects of an intratumoral injection of mda-7 (IL24; INGN 241) in patients with advanced carcinoma: a phase I study," Mol. Ther. 11(1):149-159. The Examiner contends that these articles are either limited to direct administration of a vector containing an mda-7 gene (Tong and Cunningham), or teach systemic administration using DOTAP: Cholesterol nanoparticles, which were, according to the Examiner, not known as of the filing date of this application.

Applicant respectfully disagrees with the contention that systemic administration of gene therapy was not enabled in the art as of the filing date of the instant application. Applicant invites the Examiner's attention to the following evidence to the contrary.

First, International Patent Application No. PCT/US00/29723, Publication No. WO01/34130 by Boulikas ("Boulikas"; Exhibit A), published May 17, 2001 (and now also U.S. Patent No. 6,511,676), entitled "Therapy for human cancers using cisplatin and other drugs or genes encapsulated into liposomes," teaches the use of cationic liposomes to deliver genes to cancer cells by methods that include intravenous administration (Boulikas, pp. 24-25). Boulikas was published before the filing date of the instant invention.

Second, Shi and Pardridge, 2000, "Noninvasive gene targeting to the brain," Proc. Natl. Acad. Sci. U.S.A. 97:7567-7572 ("Shi"; Exhibit B) describes successful intravenous administration of a reporter gene-containing plasmid packaged in

the interior of neutral pegylated immunoliposomes to achieve introduction of the reporter gene into the brain. Shi was published prior to the filing date of the instant application.

Third, as regards adenovirus-mediated gene therapy, Heise *et al.*, 1999, "Intravenous administration of ONYX-015, a selectively replicating adenovirus, induces antitumoral efficacy," Cancer Res. 59:2623-2628 ("Heise"; Exhibit C) teaches that intravenous administration of the selectively replicating adenovirus ONYX-015 was successful in achieving an anti-tumor effect in mice. Heise was published prior to the filing date of the instant application. A P.T.O 1449 form listing Boulikas, Shi and Heise is submitted herewith.

Boulikas, Shi and Heise demonstrate that when the present application was filed, systemic administration of gene therapy was enabled. Even if, *arguendo*, intravenous gene therapy were not perfected, this does not undermine the sufficiency of the specification toward satisfying the legal standard. Enablement "does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect" Glaxo Group Ltd. v. Tera Pharmaceuticals, No. C.A. 02-219 GMS, 2004 WL 1875017 (D. Del. Aug. 20, 2004) (citing CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338 (Fed. Cir. 2003)).

For all these reasons, the rejection should be withdrawn and not applied to the newly-added replacement claims.

3. **The Claims Do Not Constitute Obviousness-Type Double Patenting**

Claims 1, 3, 4, 8, 10, 11, 13, 14 and 18 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 ("the '137 patent") in view of Saison-Behmoaras *et al.*, 1991, EMBO J., 1991; 10(5):1111-1118 ("Saison-Behmoaras").

Additionally, claims 1, 6, 7, 9, 11, 16, 17 and 19 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 in view of the '137 patent and further in view of WO 97/16547 A1 to Roth *et al.* ("Roth").

The Examiner alleges that one of ordinary skill in the art would have been motivated to combine the '137 patent and Saison-Behmoaras to achieve the claimed invention. However, there is a lack of suggestion or motivation to combine these references. The method claimed in the '137 patent exhibits success in suppressing growth in cancer cells of the breast, central nervous system, cervix, colon, prostate, and connective tissue. Saison-Behmoaras teaches the anti-proliferative effect of an antisense-*ras* oligonucleotide which inhibits translation of *ras*-specific mRNA when hybridized to a *RAS* nucleic acid molecule. However, because the patent teaches MDA-7's ability to work independently to suppress growth, the invention does not suggest that MDA-7 requires an additional element such as *ras* inhibition in order to improve functionality in certain types of cancers, such as pancreatic cancer. Similarly, Saison-Behmoaras does not teach or suggest the combination of MDA-7 and *ras* inhibition.

Furthermore, the Examiner notes that combination of references useful for the same purpose with the objective of forming a third composition to be useful for the

same purpose constitutes double patenting. However, the present invention results in a synergistic effect between the MDA-7 and the *ras* inhibition that was previously unknown and unanticipated by the cited references. Therefore, the result achieved by the methods claimed in the present invention is not suggested by either of the cited references.

Roth teaches the use of an adenoviral vector to deliver and express an antisense oligonucleotide in a cancer cell. The Examiner suggests that Roth's reference to the potential to combine antisense therapy with known methods of gene therapy constitutes obviousness-type double patenting in light of the present invention. However, Roth suggests the combination of anti-K-*ras*-targeted therapies and other "tumor-related" genes or "antibody-based gene therapy treatment." Roth does not suggest the combination of anti-*ras* and the nucleic acid complement of a protein such as MDA-7 and as such does not render obvious the synergistic anti-proliferative effect realized by the present invention.

Accordingly, the claims do not constitute obviousness-type double patenting. For these reasons, the rejection should not be maintained or applied to the newly-added replacement claims.

4. **The Claims Are Not Obvious**

Claims 1, 3, 4, 8, 10, 11, 13, 14 and 18 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over the '137 patent in view of Saison-Behmoaras *et al.* The '137 patent teaches a method comprising introducing a nucleic acid including MDA-7 gene or gene product into a cancerous cell in order to reverse the cancerous

phenotype. Saison-Behmoaras *et al.* teaches an antisense-*ras* oligonucleotide that hybridizes to a *RAS* nucleic acid molecule and thereby inhibits translation of *ras*-specific mRNA.

Moreover, claims 1, 6, 7, 9, 11, 16, 17 and 19 are rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,710,137 in view of Saison-Behmoaras et al. and further in view of WO 97/16547 A1 to Roth et al.

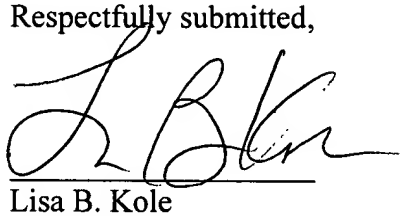
For the reasons set forth above regarding the obviousness-type double patenting rejection, neither the cancelled claims nor their counterparts in the newly-added replacement claims are obvious. There is a lack of motivation or suggestion to combine the disclosure of the '137 patent with Saison-Behmoaras in order to achieve the synergistic effect realized by the present invention. In particular, the '137 patent describes the ability of MDA-7 to independently suppress proliferation of cancer cells, whereas the present invention combines the effect of MDA-7 with *ras* inhibition in order to realize an anti-proliferative effect in cancers that had previously been unresponsive to conventional treatment. Notably, neither the '137 patent nor Saison-Behmoaras suggest to one of ordinary skill in the art that such combination is necessary or desirable. Roth teaches the use of an adenoviral vector to deliver and express an antisense oligonucleotide in a cancer cell, but does not provide the requisite motivation to combine the biological effects of MDA-7 with concurrent *ras* inhibition in order to render obvious the present invention.

For the aforementioned reasons, the claims are not obvious and the rejection should not be maintained or applied to the newly-added claims.

5. **Conclusion**

For the foregoing reasons, it is respectfully requested that claims 51-81 be allowed. An early allowance is earnestly requested.

Respectfully submitted,



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